

Philadelphia College of Osteopathic Medicine DigitalCommons@PCOM

PCOM Physician Assistant Studies Student
Scholarship

Student Dissertations, Theses and Papers

2019

Is Lifitegrast 5.0% Ophthalmic Solution Effective in Improving Eye Dryness and Safe, in Terms of Ocular Adverse Effects, in Adults 18 Years or Older with Dry Eye Disease?

Aubrey E. Cole

Philadelphia College of Osteopathic Medicine

Follow this and additional works at: https://digitalcommons.pcom.edu/pa_systematic_reviews



Part of the [Otolaryngology Commons](#)

Recommended Citation

Cole, Aubrey E., "Is Lifitegrast 5.0% Ophthalmic Solution Effective in Improving Eye Dryness and Safe, in Terms of Ocular Adverse Effects, in Adults 18 Years or Older with Dry Eye Disease?" (2019). *PCOM Physician Assistant Studies Student Scholarship*. 470.
https://digitalcommons.pcom.edu/pa_systematic_reviews/470

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

Is lifitegrast 5.0% ophthalmic solution effective in improving eye dryness and safe, in terms of ocular adverse effects, in adults 18 years or older with dry eye disease?

Aubrey E. Cole, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not lifitegrast 5.0% ophthalmic solution is effective in improving eye dryness and safe, in terms of ocular adverse effects, in adults 18 years or older with dry eye disease (DED).

Study Design: Systematic review of three primary double-blinded, randomized placebo-controlled trials that were published in peer-reviewed journals between 2014-2017.

Data Sources: Studies were obtained through the PubMed database based on relevance to the clinical question and evaluation of patient-oriented outcomes.

Outcomes Measured: Efficacy of lifitegrast treatment was measured based on the eye dryness score (EDS) obtained from a subject-reported symptom assessment using a 7-item visual analog scale. Safety of treatment was measured through investigator safety assessments and recording of adverse events conducted at study visits.

Results: All three analyzed randomized control trials showed a greater reduction in the EDS with lifitegrast 5.0% ophthalmic solution compared to placebo. In Holland et al., the reduction in the EDS was 10.7% greater with lifitegrast compared to placebo ($p=0.0007$). In Sheppard et al., the reduction was 17.8% greater with lifitegrast ($p=0.0291$). In Tauber et al., lifitegrast showed a 12.3% greater reduction ($p<0.0001$). For the safety assessment, lifitegrast had more ocular adverse effects (OAE) than placebo, with majority being mild to moderate in severity. In Holland et al., 39.5% who received lifitegrast had OAE in comparison to 17.8% who received placebo. In Sheppard et al., 33.7% with lifitegrast had OAE compared to 16.4% with placebo. In Tauber et al., 63.5% with lifitegrast had OAE compared to 26% with placebo. The NNH was 5 in Holland et al., 3 in Sheppard et al., and 6 in Tauber et al.

Conclusions: Lifitegrast is slightly more effective than placebo in improving eye dryness, but not as safe based on the number of OAE. Lifitegrast can be considered a safe monotherapy for DED based on the efficacy of improving eye dryness and improbability of causing severe OAE.

Key Words: Lifitegrast; Dry Eye Disease; Dry Eyes

INTRODUCTION

Dry eye disease (DED) is a condition caused by inadequate quality or quantity of tear production necessary for lubrication of the eye surface which results in eye dryness, discomfort, irritation, burning, visual disturbances, and foreign body sensation. The ocular discomfort and impairment in visual acuity that occurs due to DED leads to a significant impact on quality of life. This condition can also be referred to as keratoconjunctivitis sicca, dysfunctional tear syndrome, and dry eye syndrome. Common risk factors include female gender, advancing age, hormonal alterations, systemic diseases, use of contact lenses, medications including antihistamines and anticholinergics, vitamin and nutritional deficiencies, ocular surgeries, and low environmental humidity. DED can also be associated with Sjogren's syndrome, a chronic inflammatory condition affecting lacrimal and salivary gland functioning.

The etiology of dry eyes is multifactorial and complex, resulting from a dysfunction in the interaction between the lacrimal glands, ocular surface, and the eyelids that leads to an inflammation of the ocular surface and hyperosmolarity of the tear film.^{1,2} The pathophysiology of DED can be classified as either an increased evaporative loss of tears or a decreased tear production. The increase in tear film evaporation often results from meibomian gland dysfunction, decreased blinking, or structural abnormalities of the eyelids.² Decreased tear production occurs secondary to destruction or dysfunction of the lacrimal glands.² Adequate tear production by the lacrimal glands and proper evaporation of the tear film is necessary for adequate visual acuity and cleansing of the eye surface. Any disruption in these two processes leading to inflammation of the eye surface or hyperosmolarity of the tear film causes an activation of sensory nerve fibers on the ocular surface resulting in the symptoms of eye irritation and discomfort.²

DED currently affects approximately 16.4 million people in the United States and is one of the most common reasons for ophthalmology visits.^{3,4} However, the evaluation and diagnosis of DED can also be performed in an outpatient primary care or emergency setting by physicians and physician assistants. The diagnosis is based on an evaluation of patient-reported symptoms and observation of the eyes on physical exam. On examination, notable findings include conjunctival injection, excess tearing, entropion or ectropion, blepharitis, reduction in blinking, and visual impairment on acuity testing. A referral to the ophthalmologist is recommended if the etiology of symptoms is unclear, there is no improvement or relief with treatment, or severe pain or vision loss occurs.

The overall expenses for DED continues to rise annually and are based on the cost of frequent visits to healthcare providers, pharmacologic therapy, and non-pharmacologic therapy. Overall direct and indirect annual cost to the healthcare system in the United States was estimated at \$55.4 billion, with a direct cost equivalent to \$738 per person per year.⁵ Cost to society is currently estimated at \$11,000 per patient per year.⁵ Aside from the financial burden for the treatment of symptoms, DED also accounts for lost productivity in terms of absence from work or working with discomfort or altered visual acuity.⁶

The goal of treatment of DED is to increase or supplement production of tears, slow evaporation of tears, reduce the resorption of tears, and reduce the inflammation of the ocular surface.⁷ First line treatment includes artificial tear supplementation with ophthalmic gels, ointments, and solutions, and the use of environmental strategies of coping which include frequent blinking, minimal exposure to air condition and heat, and use of humidifiers. Other treatments include nutritional supplements, topical or systemic corticosteroids, topical

cyclosporine, and punctal plugs. These current treatments specifically target symptomatic relief from DED only.

Lifitegrast 5.0% ophthalmic solution is a new topical eye drop formulation that targets the underlying ocular surface inflammation and damage that causes DED. It was recently FDA approved as an integrin antagonist that functions to decrease T cell-mediated inflammation. This method was proposed as a new treatment because it has a dual mechanism of treating the underlying pathophysiology and providing symptom relief, unlike the other current treatment options. Therefore, lifitegrast may provide better long-term symptom relief and be beneficial in patients refractory to the current treatments.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not lifitegrast 5.0% ophthalmic solution is effective in improving eye dryness and safe, in terms of ocular adverse effects, in adults 18 years or older with dry eye disease.

METHODS

The articles used for this systematic review were selected based on relevance to the clinical question and evaluation of patient-oriented outcomes. Articles were obtained through PubMed database using the keywords “Dry Eye Disease,” “Lifitegrast,” and “Dry Eyes.” The articles included were written in English and published in peer-reviewed journals between 2014-2017. Articles were excluded if published before 2008, written in languages other than English, or evaluated outcomes that were not patient oriented.

This review evaluates three primary double-blinded, randomized placebo-controlled trials (RCTs). All three trials evaluated the efficacy, based on improvement of eye dryness, and safety, based on ocular adverse effects, of lifitegrast 5.0% ophthalmic solution in comparison to

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Holland et al., 2016 ⁸	RCT	711	18-93	≥18 years old with hx of DED plus all of the following: VA ≥0.7 log _{min} angle of res from visit 1, fluorescein staining 2+ in 1+ region in ≥1 eye, VAS _{EDS} 40+ b/l, conjunctival redness +1 in at least one eye, artificial tear use 30 days before screening, and positive response (≥1 eye) meeting the following at visits 1 & 2: ICSS 0.5+ and unanesthetized Schirmer Tear Test between 1-10 mm. Immunocompetent individuals with secondary Sjögren's syndrome not on systemic steroids.	Pregnancy, hypersensitivity to product, previously in a lifitegrast trial, use of medication for blepharitis or meibomian gland disease during study, ocular infection 30 days prior to screening, significant blood loss 56 days prior to screening, ocular conditions/chronic illnesses, immunodeficiency, ocular surgery in past 12 months, laser capsulotomy in past 6 months, alcohol/drug abuse, contact use during study, and DED secondary to scarring or destruction of conjunctival goblet cells. All other ophthalmic medications were prohibited during study.	74	Lifitegrast 5.0% ophthalmic solution BID (upon waking and before bedtime) single drop each eye for 84 days
Sheppard et al., 2014 ⁹	RCT	588	20-91	≥18 years old with hx of DED, artificial tear use within past 6 months, presence of conjunctival redness, corneal fluorescein staining 2+ (any field in any eye), unanesthetized Schirmer tear test between 1-10mm, and VA ≥0.7 log _{min} angle of res b/l.	Contraindications or hypersensitivity to product, active ocular inflammation by slit-lamp exam, active ocular infection, ocular surgery in past 12 months, contact use during study, and pregnancy. All other ophthalmic medications were prohibited during study.	23	Lifitegrast 5.0% ophthalmic solution 1 drop per eye BID (morning and evening) for 84 day study period
Tauber et al., 2015 ¹⁰	RCT	718	19-97	≥18 years old with hx of DED, artificial tear use in past 30 days, VA ≥0.7 log _{min} angle of res, fluorescein staining 2+ in ≥1 eye region, conjunctival redness 1+ in ≥1 eye, EDS ≥40, and positive response (≥1 eye) meeting the following at visits 1&2: ICSS ≥0.5 and unanesthetized Schirmer tear test between 1-10mm. Immunocompetent individuals with secondary Sjögren's syndrome not on systemic steroids.	Pregnancy, contraindications or hypersensitivity to product, previous lifitegrast therapy, use of medication for blepharitis or meibomian gland disease, ocular infection within previous 30 days, blood loss in previous 56 days, ocular conditions/chronic illnesses, immunodeficiency, ocular surgery within previous 12 months, laser capsulotomy in previous 6 months, alcohol/drug abuse, contact use during study, and DED secondary to scarring or destruction of conjunctival goblet cells. All other ophthalmic medications, antihistamines, and aspirin were prohibited during study.	49	BID dosing of lifitegrast 5.0% ophthalmic solution (morning and before bed), single drop each eye

placebo. The study population includes adults over the age of 18 with a history of dry eye disease. Statistics reported in the articles included mean change from baseline, NNH, RBI, ABI, and p-values. Table 1 displays the demographics & characteristics of the included studies.

OUTCOMES MEASURED

All three RCTs measured the efficacy of lifitegrast in comparison to placebo using an eye dryness score (EDS). The EDS was obtained from a subject-reported assessment using a 7-item visual analog scale (VAS). The VAS was scored on a 0-100 scale with 0 referring to no discomfort and 100 referring to maximal discomfort.^{8,9,10} In all three studies, the 7 items included eye dryness, itching, burning/stinging, eye discomfort, foreign body sensation, pain, and photophobia. All studies also asked participants to subjectively rate each of these items on a horizontal scale from 0-100 with a single score for both eyes. This efficacy assessment was completed on day -14 (screening visit), 0, 14, 42, and 84. The primary efficacy point of the Holland and Tauber studies was the EDS obtained from the VAS. In the Sheppard study, the EDS obtained from the VAS was a supportive subjective efficacy end point.

The safety of lifitegrast compared to placebo was also measured throughout each of the three RCTs. Investigator safety assessments and recordings of adverse ocular effects were conducted at all study visits after the first dose of lifitegrast. The investigator of each study assessed the self-reported adverse ocular effects of the study drug and placebo for severity. The severity was rated as mild, moderate, or severe. The most common ocular adverse events that were reported by participants included reduced visual acuity, instillation site irritation/burning, and instillation site reaction.^{8,9,10} This systematic review will focus on the results from day 84 of each of the trials.

RESULTS

The efficacy and safety of lifitegrast 5.0% ophthalmic solution in comparison to placebo was evaluated in all three RCTs. The study period for each of the trials was 12 weeks in duration. Majority of the participants in each of the trials were female and Caucasian. In all three RCTs, participants in the lifitegrast group received a single drop of lifitegrast 5.0% ophthalmic solution in each eye twice daily, once upon wakening and once before bedtime, for 84 days. Participants in the placebo group followed this same schedule with a matched placebo ophthalmic solution. At the beginning of each of the trials, participants were given a vial of the investigational product or placebo. Participants returned the vial at each visit for assessment of compliance with treatment. In all RCTs, participants who discontinued the study were analyzed using the last observation carried forward.

In the Holland et al. study, 711 participants between the ages of 18 to 93 with a history of DED were included in the study and randomized into the lifitegrast group (n=355) or the placebo group (n=365).⁸ Six hundred and thirty-seven participants completed the trial. Of the participants, 96.5% in the lifitegrast group and 97.6% in the placebo group were compliant with treatment. Participants were considered noncompliant if they took less than 20% or more than 80% of the expected treatment doses between visits and were withdrawn from the study if this occurred twice.

The mean change in baseline of the EDS on day 84 of the trial was approximately -37 for the lifitegrast group (54.2% reduction) and -30 for the placebo group (43.5% reduction). This resulted in a treatment effect of 7 which indicated that participants in the lifitegrast group had a 7-point greater reduction (10.7%) in the EDS from baseline than the placebo group. The treatment effect was statistically significant, indicated by a p-value of 0.0007, and precise, with a narrow 95% CI of 3.04-11.28.⁸ Refer to Table 2 for the efficacy results of this study.

In the Holland et al. study, the number of overall ocular adverse effects in the lifitegrast group was greater than the placebo group, as shown in Table 3. Of the participants, 17.8% in the placebo group and 39.5% in the lifitegrast group reported ocular adverse effects ranging in severity of mild, moderate, or severe. Of the ocular adverse effects in the lifitegrast group, 31.7% were mild, 7.3% were moderate, and 0.6% were severe. According to the NNH, for every 5 patients treated with lifitegrast, 1 additional person will have a mild, moderate, or severe ocular adverse effect. The safety results of this study are reported in Table 4.

Table 2: Comparison of Efficacy of Lifitegrast vs Placebo based on the Mean Change from Baseline of the EDS

RCT	Mean Change from Baseline on day 84 (Lifitegrast)		Mean Change from Baseline on day 84 (Placebo)		Treatment Effect			
	Numerical	Percent	Numerical	Percent	Numerical	Percent	95% CI	P-value
Holland et al. ⁸	-37	54.2%	-30	43.5%	7	10.7%	3.04-11.28	0.0007
Sheppard et al. ⁹	-15.2	37.8%	-10.6	25.5%	4.6	12.3%	-	0.0291
Tauber et al. ¹⁰	-35.3	50.7%	-22.75	32.9%	12.55	17.8%	8.51-16.7	<0.0001

The Sheppard et al. study included 588 participants between the age of 20-91 years old with a history of DED. Five hundred and sixty-five participants completed the study. Participants were randomized into the placebo group (n=295) and the lifitegrast group (n=293).⁹ The mean change from baseline on day 84 of the trial was -10.6 for placebo (25.5% reduction) and -15.2 for lifitegrast (37.8% reduction). The treatment effect was 4.6, indicating a 4.6-point greater reduction (12.3%) in EDS with lifitegrast. The treatment effect was statistically significant based on the p-value of 0.0291.⁹ The efficacy results of this study are shown in Table 2.

Lifitegrast was shown to cause more mild, moderate, and severe adverse ocular effects than placebo. Of the participants in the lifitegrast group, 63.5% developed ocular adverse effects,

in comparison to 26% in the placebo group, as shown in Table 3. Of the participants in the lifitegrast group who developed ocular adverse effects, 56% were mild, 7% moderate, and 0.5% severe. The calculated NNH indicated that 1 additional person will develop adverse ocular effects for every 3 treated with lifitegrast. The safety results of this study are shown in Table 4.

Table 3: Percentage of Participants who Experienced Ocular Adverse Effects (Combination of Mild, Moderate, and Severe)

RCT	Lifitegrast	Placebo
Holland et al. ⁸	39.5%	17.8%
Sheppard et al. ⁹	63.5%	26%
Tauber et al. ¹⁰	33.7%	16.4%

In the Tauber et al. study, 718 subjects from the ages of 19 to 97 years old with a history of DED were analyzed. Participants were randomized into the placebo group (n=360) or the lifitegrast group (n=358).¹⁰ Forty nine of the total participants discontinued the study before day 84. Of the participants, 95.5% in the placebo group and 93% in the lifitegrast group were compliant with treatment. Participants were considered noncompliant if greater than 20% of the expected dose was missed since the previous visit or greater than 120% of the expected dose was taken.

The mean change from baseline on day 84 was -22.75 in the placebo group (32.9% reduction) and -35.3 in the lifitegrast group (50.7% reduction), resulting in a treatment effect of 12.55. This indicates that participants in the lifitegrast group had a 12.55-point (17.8%) greater reduction from baseline in the EDS than those in the placebo group. The treatment effect was significant based on the p-value of <0.0001 and precise, based on the 95% CI of 8.51-16.70.⁹ The efficacy results of this study are shown in Table 2.

In terms of safety, lifitegrast caused mild, moderate, or severe adverse ocular effects in 33.7% of participants in comparison to 16.4% in the placebo group, as shown in Table 3. Of the

ocular adverse effects that occurred in the lifitegrast group, 84% were mild, 8.6% were moderate, and 1.7% were severe. According to the NNH, for every 6 patients treated with lifitegrast, 1 additional person will develop an adverse ocular effect. The safety results of this study are reported in Table 4.

Table 4: Safety Analysis of Lifitegrast vs Placebo

RCT	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Holland et al. ²	1.213	0.217	5
Sheppard et al. ⁸	1.44	0.375	3
Tauber et al. ⁷	1.055	0.173	6

DISCUSSION

Lifitegrast, also known by the brand name Xiidra, is a new treatment for the symptoms of dry eye disease that was approved by the FDA in July of 2016 for individuals 17 and older.

There are currently no other indications for the use of this drug. Lifitegrast is an integrin antagonist that functions to decrease T-cell mediated inflammation, thought to cause DED.^{8,9,10} It is a 5.0% ophthalmic solution that comes in a single use container and currently costs around \$600 per 30-day supply package in the United States. The current dosing regimen is 1 drop in each eye every 12 hours. Contact lens users are advised to remove the lenses before application of the solution and wait 15 minutes before reinsertion. Contraindications include hypersensitivity to lifitegrast or the drug formulation. The most common adverse effects noted include dysgeusia, irritation at the application site, and decreased visual acuity.^{8,9,10}

Lifitegrast was shown to be slightly more effective in treating eye dryness in compared to placebo. All three trials showed a small treatment effect based on the mean change from baseline of the EDS from the self-reported VAS. In each trial, the treatment effect was statistically significant based on the p-value. According to the NNH and the comparison of the percent of

individuals with ocular adverse effects between the study groups, lifitegrast was shown to be less safe than placebo. Although more participants in the lifitegrast group had ocular adverse effects and the value for the NNH was small in all studies, the ocular adverse effects were mild to moderate with very few cases being severe. In addition, the adverse effects were not unexpected, and the most common effects were irritation/burning and site reaction with application, which is common with any topical ophthalmic solution. The studies did not show any local or systemic infection from lifitegrast or any long-term effects that would impair quality of life. Based on this information, lifitegrast appears to be a generally safe treatment method. It can be concluded that lifitegrast is effective in treating eye dryness and is generally safe in individuals 18 and older with DED.

Although each of the studies displayed that lifitegrast was effective in improving eye dryness in individuals with DED, there were limitations based on the populations specifically studied. Majority of participants in all three trials were Caucasian and female. This caused limitation in the generalizability of the treatment effect since different races and gender were not evaluated equally. Also, all three RCTs only included individuals actively or recently using artificial tear substitutes. The Holland and Tauber RCTs only included individuals with DED that had used artificial tears for symptomatic relief at least 30 days prior to the study and the Sheppard study only included those who used artificial tears in the past 6 months. Therefore, individuals who had discontinued use of artificial tears in the past and were not currently or recently using artificial tears were excluded from these RCTs. Reasoning for previous discontinuation of treatment may have been due to ineffective symptom relief from other methods. With the use of this criteria for participant selection, individuals with long term or advanced dry eye disease may have been excluded.

Other limitations were also based on the inclusion and exclusion criteria. The three RCTs prohibited contact lens use during the study period, therefore individuals who desired to use contact lenses were excluded. Consequently, the efficacy and safety of this drug cannot be applied to individuals with contact lenses based on these three RCTs. Participants were also prohibited from using additional therapy for DED with lifitegrast, including artificial tears or ophthalmic solutions, during the trial period. Therefore, the efficacy and safety of lifitegrast is only based on the sole use of lifitegrast as a monotherapy. The antagonistic or synergistic effects of lifitegrast with other treatment regimens cannot be predicted based on this systematic analysis of lifitegrast. All three of the trials included a 12-week duration of therapy with lifitegrast. This limited determination of the long-term effectiveness and safety of the use of lifitegrast for DED.

CONCLUSIONS

Lifitegrast 5.0% ophthalmic solution was slightly more effective, but not safer than placebo in all three RCTs evaluated in this systematic review. Based on the efficacy results for improving eye dryness and the low probability of severe ocular adverse effects, lifitegrast should be considered as a new monotherapy for the treatment of eye dryness in patients 18 and older with DED, especially those who fail other current treatment regimens. Future research studies should focus on a longer trial period with lifitegrast with more specific attention to the safety assessment. Research in populations with contact lenses should also be considered. Other future studies evaluating lifitegrast in combination with other treatment modalities for DED, including artificial tears, steroids, and other ophthalmic medications, are warranted to determine use of lifitegrast as an add on or combination medication.

REFERENCES

1. Li D, Chen Z, Song XJ, et al. Stimulation of matrix metalloproteinases by hyperosmolarity via a JNK pathway in human corneal epithelial cells. *Investigative Ophthalmology & Visual Science*. 2004;45(12):4302. <http://www.iovs.org/cgi/content/abstract/45/12/4302>. doi: 10.1167/iovs.04-0299.
2. Lemp MA. The definition and classification of dry eye disease: Report of the definition and classification subcommittee of the international dry eye workshop The Ocular Surface. 2007;5(2):75-92. <https://www.clinicalkey.es/playcontent/1-s2.0-S1542012412700812>. doi: 10.1016/S1542-0124(12)70081-2.
3. Farrand KF, Fridman M, Stillman IO, et al. Prevalence of diagnosed dry eye disease in the united states among adults aged 18 years and older. *Am J Ophthalmol*. 2017;182:90-98. doi: S0002-9394(17)30290-8 [pii].
4. Caffery B, Devries D, Dunbar M, et al. Improving the screening, diagnosis, and treatment of dry eye disease. *Review of Optometry*. 2015;152(6):S1.
5. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the united states: A decision tree analysis. *Cornea*. 2011;30(4):379-387. doi: 10.1097/ICO.0b013e3181f7f363 [doi].
6. Yamada M, Mizuno Y, Shigeyasu C. Impact of dry eye on work productivity. *ClinicoEconomics and outcomes research : CEOR*. 2012;4:307-312. <https://www.ncbi.nlm.nih.gov/pubmed/23091391>. doi: 10.2147/CEOR.S36352.
7. Lemp MA., Bron AJ., Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *American Journal of Ophthalmology*. 2011;151(5):798.e1. <https://www.clinicalkey.es/playcontent/1-s2.0-S000293941000841X>. doi: 10.1016/j.ajo.2010.10.032.
8. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: Results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology*. 2017;124(1):53-60. doi: S0161-6420(16)31406-3 [pii].
9. Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic

solution 5.0% for treatment of dry eye disease: Results of the OPUS-1 phase 3 study.
Ophthalmology. 2014;121(2):475-483. doi: 10.1016/j.ophtha.2013.09.015 [doi].

10. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: Results of the randomized phase III OPUS-2 study.
Ophthalmology. 2015;122(12):2423-2431. doi: 10.1016/j.ophtha.2015.08.001 [doi].